Myocardial infarction with angiographically normal coronary arteries

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Myocardial infarction with 'normal' coronary arteries (MINCA) typically occurs in the under-50s[1]. Usually there is no history of angina or previous myocardial infarction (MI), and risk factors for ischaemic heart disease (IHD) may be absent[2]. Symptoms and electrocardiographic (ECG) findings are similar to those of MI with angiographic coronary disease, though the infarct sizes tend to be smaller[3]. The rate of post-MI complications, such as malignant arrhythmias, heart failure and hypotension, is lower and the long-term prognosis is more favourable[3,4].

MINCA can be classified into four groups based on risk factors for IHD and angiographic findings:

1. No risk factors for IHD with absolutely normal coronary arteries
2. Risk factors for IHD with absolutely normal coronary arteries
3. No risk factors for IHD with mild coronary artery disease
4. Risk factors for IHD with mild coronary artery disease.

MECHANISMS

The proposed mechanisms for MINCA include coronary vasospasm, coronary thrombosis *in situ* or embolization from a distal source with spontaneous lysis, cocaine abuse, viral myocarditis, aortic dissection, hypercoagulable states, autoimmune vasculitis and carbon monoxide poisoning[4].

Atheroma

Most myocardial infarctions arise from coronary artery disease. Atheromatous plaque rupture initiates an inflammatory response in which the resulting thrombosis and superimposed vasospasm compromise coronary perfusion. With selective coronary angiography the proportion of MI patients with normal or near-normal coronary arteries is between 1% and 12%[5], depending on the definition of normal—i.e. 'no endoluminal irregularities' or 'no significant (<30%) stenosis'. In a retrospective analysis, 1.1% with proven MI had no luminal irregularities[6]. Angiograms, of course, provide only a two-dimensional silhouette of the lumen, and the extent of disease found post mortem often differs from that diagnosed angiographically[7]. In a patient with 'normal' coronary arteries, intravascular ultrasound techniques will often reveal extraluminal disease[7]; so far, however, there have been no large studies with intravascular ultrasound in MINCA. There are compensatory mechanisms which preserve luminal integrity even when the internal elastic lamina is seriously diseased[8], and such diffuse coronary disease can substantially reduce coronary blood flow in the absence of significant stenosis on angiography[9].

Hypercoagulable states

One possible mechanism for MINCA is occlusion of the vessel lumen by thrombus that subsequently lyses rapidly. Platelet aggregates have been shown to cause transmural infarction and their half-life is 10–15 minutes[10]. The evidence on hypercoagulable states is mixed. The risk of MI is above normal in people with raised plasma fibrinogen and plasminogen activator inhibitor 1[11]. However, for most clotting abnormalities, including the most common inherited thrombophilia, factor V Leiden, there is no consistent link with MI[11]. In reports suggesting some excess risk, this was mainly in people who had other risk factors for coronary artery disease[12].

Lately there has been much interest in raised levels of homocysteine as a risk factor for coronary artery disease, especially in those without other risk factors, but to our knowledge no studies have been reported in MINCA patients. A raised homocysteine is thought to increase the concentrations of factor VII and thrombin[13]. This is an important cause to identify because it can be countered by vitamin supplementation[14].

Tobacco smoking, which predisposes to coronary vasospasm and thrombosis, is one of the strongest risk factors for IHD but its contribution to MINCA is less certain. Ammann *et al*. found that the prevalence of smoking was the same in patients with MINCA as in those with angiographic evidence of coronary artery disease[6]. This was the only study in which the definition of normal angiograms was 'no endoluminal irregularity' and MI was confirmed by

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wall motion abnormalities on left ventricular angiography. Earlier studies had shown that smoking was over-represented in young males with Q-wave infarction and normal coronary arteries[4].

Emboli

The role of distal emboli in the aetiology of MINCA is controversial. Theoretically valvular heart disease, endocarditis and mural thrombosis could predispose to embolic infarcts with subsequent recanalization of the vessel lumen. In one study an increased incidence of mitral valve prolapse and mitral regurgitation was found in MINCA patients, but the results are hard to interpret because of small numbers and the frequency of minor mitral valve prolapse in the general population[4].

Coronary endothelial dysfunction

Coronary vasospasm can produce myocardial ischaemia (as indicated by ST elevation on a 12-lead ECG), but there is no certainty that arterial spasm alone can cause myocardial necrosis. Syndrome X is angina with normal coronary arteries on angiography. Although dysfunction of vascular endothelium is thought to be a mechanism in both syndrome X and MINCA, there are important differences between the two groups. Most patients with MINCA do not have angina. Syndrome X patients tend to be young women. Syndrome X involves the coronary microvasculature, whereas MINCA is associated with epicardial vessels[15]. The vasospastic disorder migraine appears to be over-represented in MINCA[6].

Certain angiotensin II type 1 receptor gene polymorphisms have been associated with an increased tendency to vasospasm in angiographically normal coronary arteries challenged with a potent vasoconstrictor[16]. A combination of factors including genetic predisposition and environmental agents could predispose individuals with normal coronary arteries to infarction. However, extraluminal disease may still be the primary underlying cause.

Cocaine use has been linked with MI in the absence of coronary artery disease. The proposed aetiology is increased myocardial oxygen demand and paradoxical coronary vasospasm and thrombosis as a result of alpha-adrenergic action[17]. The likelihood of MI and further complications is further increased by smoking, concomitant alcohol intoxication and the presence of coronary heart disease[17]. Cocaine use is an important cause to identify because beta-blockers are contraindicated (the alpha-vasoconstrictor actions of catecholamines are left unopposed). There have been no prospective studies of cocaine use by MINCA patients.

Dissection

Aortic dissection and spontaneous coronary artery dissection can result in an MI with little evidence of coronary artery disease. If aortic dissection is suspected a chest CT or transoesophageal echo is indicated to exclude the diagnosis since thrombolysis will be contraindicated. Spontaneous coronary dissection can be managed safely by stenting.

Inflammation

Mediators of acute inflammation are thought to have a key role in acute coronary syndromes; indeed, markers of inflammation can be used for risk stratification. Whether the inflammatory response is the primary trigger or secondary to plaque rupture is unclear. Some investigators have linked specific infective agents with acute coronary syndromes—*Chlamydia pneumoniae*, cytomegalovirus, *Helicobacter pylori*—suggesting that they might destabilize atheromatous plaques[18]. However, the retrospective series of Ammann *et al*.[6] (21 patients with MINCA) did not show significantly higher antibody titres to those organisms than patients with MI and abnormal coronaries—though they did have a higher incidence of febrile episodes and upper respiratory tract infections before the infarction.

Myocardial infarction with normal coronary arteries has been reported in the context of systemic lupus erythematosus (without evident vasculitis[19]) and in myocarditis[20]. Myocarditis was confirmed by endomyocardial biopsy in two individuals with MINCA preceded by a viral infection[20]. Myocarditis can mimic MI and endomyocardial biopsy combined with immunohistochemical analysis can be helpful in identification. Angelini *et al*.[21] reported 12 patients (8 male) with MI confirmed by ECG changes, cardiac enzyme rises and wall motion abnormalities on echocardiography who were subsequently found to have normal coronary arteries on angiography. Endomyocardial biopsy yielded evidence of myocarditis in 11. There were no distinguishing clinical features to suggest myocarditis: only 6 patients gave a history of previous viral illness; ECGs showed regional changes and only 3 patients had a global decrease in left ventricular function on admission. These patients were young (average 29 years old) and most had no risk factors for IHD. Viral serology was not performed in all the patients and had a low yield.

TREATMENT AND PROGNOSIS

The initial management of these patients is the standard treatment for MI—including pain relief, aspirin, thrombolysis if indicated and beta blockade. If cocaine abuse is suspected then beta-blockers are contraindicated. In young patients with MI, we recommend a urine screen for cocaine.

If absolutely normal coronary arteries are identified and a regional wall abnormality has confirmed MI, then a search

for an underlying clotting disorder is reasonable though unlikely to be fruitful. If an inherited thrombophilia is identified, anticoagulation must be considered. In what circumstances should endocardial biopsy be performed? The argument for biopsy is strongest in young patients with no risk factors for IHD (group 1) and without other identifiable cause. However, the procedure carries risks, and in most cases myocarditis is self-limiting, not requiring special treatment. Thus, the main argument for confirming myocarditis is avoidance of unnecessary treatment.

In groups 1 and 2, with an identifiable cause absent, underlying coronary artery disease is the most likely aetiology. Treatments include aspirin, a beta-blocker, a statin and an angiotensin converting-enzyme (ACE) inhibitor. Hypertension and diabetes should be well controlled and smoking should be discouraged. In group 2 some clinicians have advocated the use of calcium channel blockers, to relieve or prevent vasospasm. There is no evidence that this improves outcome. The prognosis in groups 1 and 2 is more favourable than in age and sex matched individuals with identifiable coronary artery disease: in a mean follow-up of nearly 5 years in 21 such patients there were no deaths or major cardiac events[6].

Groups 3 and 4, who have identifiable coronary artery disease on coronary angiography, should likewise be treated with aspirin, a beta-blocker, a statin, an ACE inhibitor and risk factor modification. Their worse prognosis (annual death rate 1.5% and major recurrence rate 2.7%) justifies a more rigorous approach to blood pressure, cholesterol and glycaemia.

CONCLUSION

The most likely underlying disorder in myocardial infarction with normal angiograms is coronary artery disease, which predisposes the artery to vasospasm and thrombosis. Without intravascular ultrasound it is not possible to say that coronary artery disease is absent; the atheroma formation may be predominantly extraluminal. The younger age group may reflect the natural progression of disease—extraluminal in the initial stages, as the vessel wall compensates to maintain unrestricted luminal blood flow. The prognosis in this group is more favourable than in patients with angiographic disease. In addition to intravascular ultrasound, MRI deserves investigation for assessing the burden of extraluminal disease. Another promising technique is electron beam computed tomography for detection of coronary artery wall calcification, a marker for complex atherosclerotic lesions[23].

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